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Bench-to-Bedside

Infection-Specific HIV Antibody Assay

by Fran Pollner

HIV-1 Infections During Vaccine Trials: Identifying New Peptides for the Differential Diagnosis of HIV-1 Infection in the Face of Vaccine-Generated Antibodies
Hana Golding, CBER; Barney Graham, VRC

Fran Pollner

Hana Golding and Barney Graham

Within two to three years—at most—an array of HIV vaccines currently in the pipeline will be moving into large-scale Phase III clinical trials involving thousands and thousands of volunteers. The ability to distinguish vaccine-generated antibodies from actual early HIV infection among these multitudes will be imperative, says Hana Golding.

It will also be a reality.

Thanks to a Bench-to-Bedside award, Golding, chief of the Laboratory of Retrovirus Research at the Center for Biologics Evaluation and Research, FDA, and her team (postdoc Surender Khurana and fellow James Needham) have developed an alternative assay that, unlike currently licensed HIV-1 detection kits, is designed to yield a negative result in the face of vaccine-generated HIV-1 antibodies.

And on a more global level, as the numbers of trial participants balloon, false-positive test results can become a major problem for blood and plasma collection centers, as well as a source of discrimination in employment, insurance, and other facets of life.

"We have identified to our satis-

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AIDS-Targeted Bench-to-Bedside Projects

NIH Investigators Tackle the Spectrum Of Persistent and Emerging HIV Challenges

Seeking a Less Perfect Host

by Karen Ross

Therapeutic Targeting of a Virally Regulated Host Cell Molecule in HIV Infection
Sharon Wahl, NIDCR; Henry Masur, CC; Michael Sporn, Dartmouth; Nancy Vázquez, NIDCR

Despite a fire early this year that filled their lab in Building 30 with smoke and forced them to relocate for several months, Sharon Wahl, chief of the Oral Infection and Immunity Branch, NIDCR, and Senior Fellow Nancy Vázquez have made great progress on the bench side of their project.

Karen Ross

Sharon Wahl (left) and Nancy Vázquez

They are interested in host cell proteins that are required for HIV infection. These proteins are excellent therapeutic drug targets, says Vázquez, because unlike viral proteins, they are unlikely to mutate and become drug resistant.

Wahl and Vázquez are focusing on macrophages as reservoirs of HIV and as targets of the virus during the later stages of AIDS when most of the CD4+ T-cells (the more famous targets of HIV) have already succumbed.

Reasoning that the levels of cellular proteins that interact with HIV would increase during infection, Wahl and Vázquez, together with colleague Teresa Wild, used a cDNA microarray to monitor changes in gene expression throughout the macrophage transcriptome during the course of infection of macrophages by HIV.

Indeed, they found two waves of increased gene expression: One occurred shortly after the initial contact of the virus

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Salvage Therapy

by Fran Pollner

Use of 5-Fluorouracil (5-FU) in Combination with Antiretroviral Drugs as a Salvage Strategy to Overcome Drug Resistance in Heavily Treated HIV-Infected Pediatric Patients
Lauren Wood, NCI; Chad Womack, VRC

Fran Pollner

Lauren Wood

As a result of advances in treatment, perinatal HIV infection is now a rare event in the United States, and pediatric HIV/AIDS is now a chronic disease, observes Lauren Wood, who over the past 12 years at NCI has watched her HIV-positive patients move from childhood to adolescence and on to young adulthood, the beneficiaries of ever-improving antiretroviral strategies.

The problem now is drug resistance. Some of Wood's "babies"—"now driving, graduating from high school, and getting tattoos"—are also starting to fail on highly active antiretroviral therapy (HAART).

"We need salvage regimens that will stave off progression to AIDS, invasive opportunistic infections, or death," says Wood, of the HIV & AIDS Malignancy Branch, NCI, and co-director of the NCI Pediatric Outpatient Clinic. She thinks the anticancer agent 5-fluorouracil (5-FU) may augment the effectiveness of certain HAART regimens and, pending bench data

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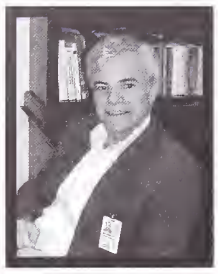
Increasing Diversity in the NIH Scientific Staff: Next Steps



Michael Gottesman

It has been 10 years since I wrote an essay in the *Catalyst* pointing out the need to improve racial and sexual diversity among NIH's principal investigators and suggesting several steps that we would take to make improvements (*The NIH Catalyst*, July 1994, "Increasing Diversity in the NIH Scientific Staff" <**http://www.nih.gov/catalyst/back/94.07/DDIR.html**>).

These steps included an institutional dedication to finding qualified scientists from diverse backgrounds, requirements that search committees include underrepresented scientific members, development of training programs to increase the pool size of qualified applicants, and fostering an atmosphere that would encourage minority scientists and women to apply for positions as independent investigators at NIH.

Despite these efforts, the picture for most minorities at NIH is only incrementally improved, and for African-American scientists has actually deteriorated (see Tables 1 and 2).

This situation has occurred among our principal investigators despite evidence that NIH as a whole over a similar time period (1990–2000) has been more effective in hiring doctoral-level minority scientists into management or scientific oversight positions (see Table 3).

Why have we failed to make more progress, and what can we do about it?

Because progress is more evident among our scientists of Hispanic or Asian-Pacific Islander ancestry, I will focus my comments on women, African-American, and Native American scientists. Women make up approximately 50 percent of the postdoctoral pool in biological sciences at NIH and elsewhere, but either choose not to compete or do not compete as successfully as men for jobs as tenure-track investigators.

In addition, women leave the tenure-track more frequently than men, for reasons we have not yet fully determined, but not because they are less successful once they get to the Central Tenure Committee for consideration.

Under the chairmanship of Joan Schwartz, the Second Task Force on the Status of Intramural Women Scientists at the NIH is exploring these issues and promises to release a report defining the problems and suggesting ways to improve representation of women among both our tenure-track and tenured investigators.

There are two main problems that re-

Table 1. Demographics of Tenure-Track Investigators By Sex and Race/Ethnicity

	1994	2004
Total	157	300
Women	44 (28%)	82 (27%)
African American	7 (4.5%)	5 (1.7%)
Hispanic	7 (4.5%)	17 (5.7%)
Native American	1 (0.6%)	0
Asian/ Pacific Islander	16 (10.2%)	65 (21.6%)
White	126 (80%)	213 (71%)

Table 2. Demographics of Senior Investigators By Sex and Race/Ethnicity

	1994	2004
Total	1145	952
Women	189 (16.5%)	178 (19%)
African American	8 (0.7%)	10 (1.1%)
Hispanic	17 (1.5%)	24 (2.5%)
Native American	1 (0.1%)	2 (0.2%)
Asian/ Pacific Islander	82 (7.2%)	81 (8.5%)
White	1038 (91%)	835 (88%)

Table 3. Doctoral Level NIH Scientific Staff (>GS13)

	1990	2000
Total	1480	2191
Women	263 (17.7%)	726 (33.1%)
African American	38 (2.5%)	91 (4.1%)
Hispanic	20 (1.4%)	56 (2.6%)
Native American	1 (0.1%)	6 (0.3%)
Asian/ Pacific Islander	93 (6.2%)	243 (11.1%)

duce representation of African-American and Native American scientists at NIH. The first is that there are few such applicants for positions, reflecting not only the smaller pool size of doctoral level minorities compared with their representation in the population as a whole, but also a strong perception among African-Americans and Native Americans that NIH is not a welcoming environment for them.

Second, African-American scientists in particular leave the tenure-track at a higher rate than other investigators, reflecting both their recruitment to jobs outside of NIH (a positive development for these scientists) and inadequate mentoring and career support at NIH.

Unfortunately, the continuing failure of NIH to improve its minority representation understandably reinforces this perception. To do better, we need to work much harder to change both the reality and the perception.

The Diversity Council is partnering with the Office of Intramural Research to identify defects in the search process that affect recruitment of a diverse population of principal investigators.

One clear finding is that our search committees are too often "selection committees" that screen and make recommendations regarding individuals who present themselves as applicants. We need to encourage these committees to be more proactive in their efforts to identify candidates and invite them to apply.

Additional recommendations about how to improve our search processes will be forthcoming.

One encouraging sign is that many of our training programs have been extremely successful in finding outstanding candidates from diverse backgrounds, especially the Undergraduate Scholarship Program for disadvantaged students and the postbaccalaureate NIH Academy program dedicated to the elimination of domestic health disparities.

These programs and others throughout NIH have created a cadre of talented, highly trained individuals who are knowledgeable about NIH and are likely to be interested in scientific careers here. We must do everything we can to foster the careers of these individuals and encourage them to return to NIH to be part of our future scientific staff.

The Black Scientists Association at NIH has proved to be a major asset in encouraging minority scientists to pursue scientific positions at NIH at all levels and in helping to support minority scientists once they get here (see "A Decade of Growth: Quality Outshines Quantity," page 8).

In addition, the BSA has suggested several new programs to encourage career development among minority scientists at NIH, including interdisciplinary training programs. With the support of our scientific leadership, we hope to implement these ideas.

NIH leadership is strongly behind efforts to improve workplace diversity, and my office will be increasing its efforts to improve diversity at NIH. But this problem cannot be solved from the top down. We all need to be part of the solution by encouraging our colleagues to apply for NIH positions and by creating an atmosphere that is conducive to the success of all scientists at NIH.

I welcome your comments and suggestions.

—Michael Gottesman
Deputy Director for Intramural Research

NIH Hispanic Scientist Day

As part of the 2004 Hispanic Heritage Month Celebrations, the NIH-Hispanic Employee Organization (NIH-HEO) is organizing the fifth NIH Hispanic Scientist Day, which will be held **October 13 from 8:30 to 11:30 a.m.** in the Lipsett Auditorium, Building 10.

Victor Marquez, chief of the Laboratory of Medicinal Chemistry, NCI, will present "Zebularine: A Molecule Destined for Clinical Trials as a Candidate for Cancer Epigenetic Therapy: The Magic of its Chemistry and Biology," followed by a brief presentation by Carlos Caban, NIH Extramural Programs Policy Officer, OD, titled "Opportunities for NIH Extramural Funding". There will be time for questions.

A poster session and reception will follow the scientific presentation, from 10:00 to 11:30 a.m.

This event seeks to promote and showcase the contributions of the Hispanic and Hispanic-American scientists at NIH, FDA-CBER, and USHUS. ■

NCCAM Lecture: Herb-Drug Interactions

The sixth in the NCCAM Distinguished Lectures series is set for **October 26, 2004, from noon to 1:00 p.m.** in Masur Auditorium, Building 10. Steven Kliewer, professor of molecular biology and pharmacology at the University of Texas Southwestern Medical Center, Dallas, will speak on "Reverse Herbology: Predicting and Preventing Adverse Herb-Drug Interactions," including recent findings on the activation of the PXR receptor by St. John's wort.

The lecture will be videocast at **<http://videocast.nih.gov>** and sign language interpretation will be provided. For more information or for reasonable accommodations, call 301-594-5595 or the Federal Relay at 1-800-877-8339. More information about the series can be found at **<nccam.nih.gov/news/lectures>**.

Seminar: Women and Obesity

Another in the Women's Health Seminar Series occurs Thursday, **November 4, 2004, from 1:00 to 3:00 p.m.** in the Lipsett Amphitheater, Building 10. Sponsored by the Office of Research on Women's Health, the topic is "Women and Obesity."

Note: The lecture on "Identifying the BMI of Risk for African Americans," presented by NIDDK's Anne E. Sumner on September 17, 2004, under the auspices of the Women's Health Special Interest Group is available for viewing at

<http://videocast.nih.gov>

Space Considerations

The Office of Research Facilities Development and Operations has launched a website at **<http://orf.od.nih.gov>**. A service-based navigation bar and a Google-powered search tool lead to:

- Guidance on appropriate use of IC funds for renovations
- How NIH defines and calculates square feet
- Maintenance request forms
- Scheduled utility shutdowns in each building
- Guidance on plans for renovations of space
- A move-in checklist for ICs
- The NIH Master Plan, Waste Disposal Guide, and other documents
- Building assignments and contact information for facility managers and real estate specialists

New content development is ongoing, and suggestions are welcome. ■

Seeking a Less Perfect Host

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with its receptor on the cell membrane; the other occurred later, after the virus had commenced replication and was accumulating inside the macrophage.

Wahl and Vázquez then focused in on one gene they considered particularly exciting because they found that preventing the spike in its expression inhibited the infection process.

Karen Ross

Sharon Wahl (left) and Nancy Vázquez

Henry Masur

Although the gene is normally involved in programmed cell death or regulation of cell division, its exact function in HIV infection is still not understood. The researchers speculate that it may promote HIV infection by aiding viral replication. They are now trying to identify other proteins, both viral and cellular, that interact with it.

Their research got an unexpectedly direct connection to the bedside through a collaboration with Michael Sporn, a former NCI lab chief now at Dartmouth College in Hanover, N.H. Sporn is interested in a class of compounds found in plants called triterpenoids that have been widely used in traditional Chinese medicine to fight inflammation and cancer. Sporn's colleagues at Dartmouth synthesize new triterpenoid analogs, and his lab tests their properties in cell culture. He had sent one of his synthetic compounds to Wahl to use in an unrelated project. She and Vázquez decided to try the drug in the HIV-macrophage system and, to their delight, it prevented the HIV-induced increase in expression of the gene they had been studying, and it blocked infection.

Together with Henry Masur, chief of the Critical Care Medicine Department at the Clinical Center, Wahl and Vázquez are now designing a clinical trial for this drug. Because the drug also has promising anticancer activity, the team is interested in testing it in HIV patients who have lymphoma. Lymphoma, says Masur, is overrepresented in patients with HIV and has become even more prevalent in recent years as HIV patients have been living longer.

Anticancer therapy for HIV-infected patients with lymphoma needs improvement, Masur says, noting that current regimens are very toxic and interfere with antiretroviral regimens because of cross-toxicities and drug interactions.

At the moment, the Rapid Access to Intervention Development (RAID) program at NCI is working on scaling up production of the drug, and more in vitro studies are planned. Phase I trials in humans will be conducted first in patients who have lymphoma only. If the drug appears to be effective against lymphoma, the trial will be expanded to include patients with HIV and lymphoma.

Wahl, Vázquez, and Masur all applaud the Bench-to-Bedside Award program for bringing together basic and clinical researchers and stimulating interdisciplinary and cross-institute research—and for providing funding for new initiatives that might otherwise not have been able to get going. "We hope it will be expanded," Masur says. ■

The Inside Story

by Karen Ross

Imaging Probe for the in Vivo Assessment of HIV-1 Dynamics
Michele Di Mascio, NIAID; Sunil Pandit, CC; Narasimhan Danthi, CC; King Li, CC; Tomozumi Imamichi, NIAID-SAIC; Cliff Lane, NIAID

This project, headed by Michele Di Mascio, applies nuclear medicine technology to virology with the goal of developing a noninvasive way of tracking HIV in the body. Di Mascio, a biological systems modeler, is based at the Biostatistics Research Branch, NIAID.

Currently, the only way to identify HIV-infected tissues is through biopsies, procedures that are difficult for patients and yield only a limited view of the scope of infection.

The ability to see HIV throughout the body would clearly provide greater understanding of how HIV acts upon organs and how its profile changes over time. It would also help physicians find and target therapy to pools of virus that have evaded antiretroviral drugs, says Sunil Pandit, one of the CC originators of the study and now a leader in the bioengineering and genomic applications group, Heart and Vascular Diseases Division, NHLBI.

The project is highly challenging, says Di Mascio, but the initial results are quite promising.

The team set out to introduce into the body a radioactively labeled molecule that binds specifically to a protein of interest. Doctors then use imaging equipment such as a gamma camera or PET to detect the radioactive signal. The first hurdle is to choose the optimal molecule and then label it without compromising its ability to bind to its target, in this case, sites of active HIV infection.

Karen Ross

Michele Di Mascio

Karen Ross

Sunil Pandit

A team from the CC Laboratory of Diagnostic Radiology Research (King Li, director, and Narasimhan Danthi, staff scientist) and NIAID (Tomozumi Imamichi, senior scientist, NIAID/SAIC-Frederick Laboratory of Human Retrovirology, and Cliff Lane, NIAID clinical director) has focused on a class of anti-HIV drugs called fusion inhibitors, the first of which was recently approved by the FDA.

These drugs block HIV infection of new cells by preventing the merger of the viral and cell membranes.

In the presence of fusion inhibitors, HIV becomes trapped, stuck to the cells it was on the verge of infecting with the drug bound to the junction between cell and virus. A radiolabeled fusion inhibitor, therefore, has the potential to be an excellent tool to monitor HIV infection in a patient.

So far the group has successfully attached a radioactive molecule to a fusion inhibitor and has shown that the drug is still effective at blocking viral infection in cultured cells, suggesting that the label did not radically alter its binding properties.

The next step is to test the strategy in monkeys infected with SHIV, a hybrid of HIV and its monkey counterpart, SIV. The CC's Esther Lim and NIAID's Malcolm Martin and Tatsuhiko Igarashi, are heading up this effort. ■

AIDS-Targeted Bench-to-Bedside Projects

Recombination and Resistance

by Karen Ross

Role of Recombination in HIV-1 Drug Resistance in Vitro and in Vivo
Frank Maldarelli, Sarah Palmer, Wei-Shau Hu, John Coffin, NCI; Michael Polis, NIAID; Jo Ann Mican, NIAID

The mechanisms and nature of HIV drug resistance are the focus of a Bench-to-Bedside project that is composed of a bench team at NCI-Frederick and a bedside team at the Clinical Center. The project is headed by John Coffin, director of the HIV Drug Resistance Program at NCI-Frederick.

Researchers suspect that drug resistance arises because HIV does a shoddy job of replication, accumulating several mutations during each cycle. When patients receive antiretroviral drugs, the overwhelming majority of the virus succumbs, but a few virus particles, with just the right combination of mutations, survive drug treatment and quickly replenish the viral population. Thus, despite the use of many seemingly effective anti-HIV drugs, patients so far cannot be cured.

This model strongly predicts that an untreated HIV-infected individual harbors a genetically diverse population of virus. But just how diverse is the viral population, and how quickly does its genetic makeup change over time?

Karen Ross

Frank Maldarelli

Sarah Palmer

Frank Maldarelli, staff clinician in the DRP Host-Virus Interaction Unit, and his colleagues in the NIH Clinical Center—the bedside team—collected a series of samples over the course of 18 months from HIV-positive people who had not yet been treated with antiretroviral drugs. (Patients with low viral loads and relatively healthy immune systems often elect to delay treatment, Maldarelli observes.)

Sarah Palmer, manager of the DRP Virology Core Facility, and her group—the bench team—developed a new assay, known as single-genome sequencing (SGS), to analyze these samples. Unlike older methods, which can detect only the predominant viral genotypes within a sample, SGS provides an accurate picture of the full range of viral diversity.

The investigators found that viral populations were indeed diverse and that the most frequently occurring genotypes changed slowly over time, probably in response to pressure from the patient's immune system.

They were also able to verify a laboratory prediction—that HIV genomes change not only through acquiring mutations during replication but also through exchanging parts with each other, a process known as recombination.

For viruses to recombine, at least two must infect the same cell. Based on the frequency of recombination, the researchers concluded that at least 20 percent of infected cells were invaded by multiple copies of the virus, a surprisingly high number, Maldarelli says, that suggests that HIV-infected people carry large populations of virus.

The team expects these new insights into HIV genetics to help guide therapy in the future. Knowing the speed of viral diversification can inform the decision of when to initiate anti-HIV treatment, and drug combination choices can be optimized by tracking virus recombination patterns.

Stifling recombination could become a therapeutic strategy, Maldarelli says. ■

A Means to End Latency

by Karen Ross

Treatment of Drug-Resistant and Persistent HIV-1 Infection with the Designed Proteins 5-Helix and 5-Helix-PE
Dean Hamer, NCI; Joe Kovacs, NIAID

Dean Hamer (NCI), Michael Root (Thomas Jefferson University in Philadelphia), and a team of clinical investigators from the Clinical Center and NIAID led by Joe Kovacs are working on two related anti-HIV drugs called 5-Helix and 5-Helix-PE (Pseudomonas exotoxin).

These drugs are designed to combat two of the lingering problems that defy attempts to cure HIV infection: drug resistance and latent infection.

5-Helix is a fusion inhibitor, a new class of drugs that interferes with the progression of HIV infection by preventing the virus from entering new host cells. Root developed 5-Helix as part of his research into HIV-host cell interactions.

HIV, Hamer explains, uses a "protein machine" that consists of components on both the virus and cell membranes to enter cells. Once the virus has made contact with receptors on cells, the machine must snap closed "like a spring trap" in order for the virus and cell membranes to fuse. Fusion inhibitors are fragments of protein that bind to the trap and "gum it up." HIV gets stuck in an intermediate state, attached to the cell, but unable to go further.

Dean Hamer

The first and only fusion inhibitor to receive FDA approval so far, T20, is helping beat back disease in some patients whose virus is resistant to all other treatments. Unfortunately, Hamer says, after as little as one month of therapy, T20-resistant strains of HIV are already appearing. 5-Helix, however, may elude this pitfall, Hamer says. It will be difficult for HIV to acquire resistance to it because the part of the virus recognized by 5-Helix is absolutely critical for HIV function.

Mutations in this region disable the virus so severely that strains with changes significant enough to prevent 5-Helix from binding will probably not be able to survive and multiply, he explains.

This year, Hamer's group has shown that 5-Helix is indeed effective in vitro against a wide range of existing HIV variants. They are now moving into animal studies, testing 5-Helix in SCID-hu mice infected with HIV. Studies with macaque monkeys infected with SHIV, a human-simian hybrid immunodeficiency virus, are also planned.

In an effort to seek out and destroy latently infected cells, Hamer and his group have created 5-Helix-PE, which is a form of 5-Helix with an attached toxin. Because the membranes of HIV-infected cells contain the viral protein recognized by 5-Helix, the 5-Helix-PE should bind tightly and specifically to infected cells and then kill them with the toxin.

By the end of next year, the group hopes to test this approach using cells taken from infected patients.

Meanwhile, Kovacs watches from the wings. "If the preclinical findings continue to be as encouraging as they are now, we would be very excited to bring this class of drugs into clinical trials," he says.

Hamer is grateful for the Bench-to-Bedside Award program for providing the resources for the preclinical work. 5-Helix and other fusion inhibitors, he notes, are proteins, which are much more difficult and expensive to make than traditional small-molecule drugs. The award has also supported the animal experiments. ■

Salvage Therapy

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in the making, is designing a clinical protocol to demonstrate proof of principle.

Chad Womack, a senior research fellow at the VRC and the bench partner in this Bench-to-Bedside project, has been studying the resistance patterns in clinical isolates from Wood's patients—who are on a variety of antiretroviral agents—and measuring the effects of 5-FU in vitro.

The virus mutates rapidly, quickly developing resistance to the antiviral drugs it encounters, but that ability to mutate and survive in an antiviral drug environment, Womack says, may come at a price—a compromised ability to replicate.

The virus, he says, is "dancing on the edge of chaos," balancing survival through mutation against extinction through loss of replication capacity or fitness.

There is reason to believe that 5-FU will throw the virus over the edge, the researchers say.

Traditionally used as an anticancer drug, 5-FU is at the benign end of the toxicity spectrum of such agents, Wood says. As an anti-HIV agent, "it appears to alter the availability of the genetic building blocks" the virus uses to make more of itself.

Fran Pollner

Lauren Wood

Fran Pollner

Chad Womack

Specifically, 5-FU inhibits thymidylate synthetase, an enzyme that generates thymine nucleotides, natural building blocks that HIV requires for replication. Wood notes that there are data suggesting that 5-FU can improve the intracellular pharmacokinetics of two of the nucleoside analogs commonly used in HAART regimens—AZT (zidovudine) and d4T (stavudine). By lowering levels of natural building blocks, 5-FU causes a preferential incorporation of defective building blocks supplied by the phosphorylation of drugs like AZT and d4T.

Womack believes it may also push the virus to hypermutate and severely cripple the virus' replication machinery. "It's a strategy called lethal mutagenesis, and there aare other in vitro data suggesting it can be successful against HIV," he says.

Thus, the antiretroviral activity of AZT and d4T is optimized at the intracellular level without incurring the increased systemic toxicity caused by higher drug dosages, Wood notes. This point is critical, Womack adds, because many HIV-infected patients who are experiencing therapeutic failure are running out of options.

The clinical study will look at low-dose 5-FU in combination with a HAART regimen that includes either AZT or d4T in heavily treatment-experienced adolescents and preadolescents, most of whom were born with HIV, have been on therapy for 10 to 12 years, have undergone several rounds of HAART, and are failing clinically, immunologically, and/or virologically. The target enrollment is 30 patients and is anticipated to begin early next year.

A basic scientific question, says Wood, is whether virus grown out from different cellular compartments in the same individual displays a uniform resistance profile.

"We're looking at plasma, peripheral blood mononuclear cells, CD4 cells and subsets including naïve and memory cells, and monocytes/macrophages. We need to know what's happening to the virus in these different compartments as we give these drug combinations—that's why these bench studies are so critical." ■

A Therapeutic Vaccine for Children on the Road to a Prophylactic Vaccine for All

by Fran Pollner

Effect on Immune Responses and Sustainability of Viral Suppression in HIV-Infected Children of a Therapeutic Vaccination Strategy with a Multiclade HIV-1 DNA Plasmid Vaccine Prime and a Recombinant Adenovector Boost
Steven Zeichner, NCI;
Richard Koup, VRC

Children with HIV disease who are doing poorly on highly active antiretroviral therapy (HAART) are candidates for studies of new antiretroviral regimens. HIV-infected children who are doing well on HAART are candidates for a HIV-1 vaccine study.

The idea, says Steve Zeichner, of the NCI HIV & AIDS Malignancy Branch, is to immunize children still healthy enough to respond to a vaccine and before they become teenagers, who are less likely to adhere to a therapeutic regimen.

Beyond that, he says, is "the holy grail, a prophylactic vaccine—and the target population for that, ulitimately, has to be children."

Fran Pollner

Steven Zeichner

Testing this therapeutic vaccine in children "is one step toward the goal" of a prophylactic vaccine, Zeichner observes.

Richard Koup, who is at the VRC where the multiclade, multivalent vaccine was designed and is being tested in adults—a prelude to its use in children—notes that the vaccine is actually being developed with an eye toward prophylaxis.

The DNA prime and adenovector boost platforms for a vaccine that covers clades A, B, and C—at least 90 percent of infections worldwide—has the "best immunologic profile of anything we've looked at," Koup says, "and if we're going to go into a population of children, we're going in with the best possible product."

The DNA portion will likely consist of six plasmids—one each that encodes the Gag, Pol, and Nef proteins and three others that encode the envelope protein of the three clades.

Fran Pollner

Richard Koup

Zeichner and Koup, chief of the VRC Immunology Laboratory, think that the vaccine may elicit an even better immune response in children than in adults for several reasons:

- HIV-infected children may be less likely than individuals infected with HIV as adults to have pre-existing immunity to adenovirus and may have a more robust immune response than HIV-infected adults.
- Children have better functioning thymus glands and more naïve T cells available to respond to the vaccine.
- Evidence indicates that the immune system of a child is more readily reconstituted after insult.

The vaccine must go through several rounds of testing in adults before the protocol in children can be finalized and the trial

HIV Antibody Assay

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faction two epitopes that will generate antibodies only in the presence of true infection," says Golding, noting that the validity of large-scale HIV vaccine trials involving high-risk participants will depend on being able to identify quickly those who get infected. The vaccine regimen would then be halted, and they would be transferred to another arm, where any effect of the vaccine could be followed and where they might be eligible for HIV therapy, according to the standard of care at the site of the trial.

Fran Pollner

Hana Golding

Fran Pollner

Barney Graham

Without her Bench-to-Bedside collaboration with Barney Graham, chief of the Viral Pathogenesis Laboratory and director of clinical studies at the Vaccine Research Center, NIAID, this work could not have been accomplished, she says. Further support will come from OAR, DAIDS, and NHLBI.

The Quest for Epitopes

The epitopes had to meet quite specific requirements:

- They could not be components of current HIV candidate vaccines, a tricky demand because vaccine constructs have become increasingly complex as researchers have strived to expand their immunogenicity.
- They had to be epitopes that do not generate protective immunity and are therefore dispensable in formulating new candidate vaccines.
- They had to be recognized at high enough rates during early seroconversion to generate antibodies.
- They had to be highly conserved among many HIV variants, clades, and interclade recombinants in order to be useful anywhere in the world a trial takes place.

To find these epitopes, Khurana constructed a gene-fragment phage-display library expressing segments from the entire open reading frame of the HIV-1 genome. The library was used to screen sera drawn from individuals within three months of initial HIV infection to establish the early repertoire of HIV-1 antibodies. Many were already components of existing HIV detection kits.

Gag-p6 and gp41 peptides met all criteria. The gp41 peptide identified is located in the cytoplasmic tail of the envelope glycoprotein and, unlike extracellular gp41, has no neutralizing epitopes. Similarly, Gag-p6, a small part of the much larger Gag-Pol protein, shows no evidence of raising neutralizing antibodies or protective cellular immunity.

"We identified these two sequences, which to our surprise had not been described in the literature as potent inducers of antibodies," Golding says. "Somehow during acute infection, enough of these portions of the proteins is exposed to the immune system to generate antibodies, and they were recognized at very high rates by samples from very early seroconverters."

Using the peptides, the team got to work producing a new immunosorbent assay that they subjected to testing with a variety of serum panels that include all known serotypes—from many countries, including Australia, Cameroon, Uganda, and the United States. Results compared favorably with currently licensed HIV-detection kits.

What's Next

The team is now working on fine-tuning the assay, testing a second-generation of gp41 and Gag-p6 consensus peptides with even higher homology to all clades.

The assay, Golding says, is simple, rapid, and cheap, and requires no special expertise to carry out and no more than a small regular refrigerator to store the samples.

The team now has two tasks: to complete its screening of seroconverters around the world and to launch the screening of vaccinated individuals and seroconverters in HIV vaccine trials. The latter samples will come from ongoing VRC trials involving complex candidate vaccines and from already completed studies from the NIAID-funded HIV Vaccine Trials Network (HVTN).

"Here is where Barney Graham, who has been a source of advice all along, will be instrumental in the coming stages of the project and beyond the formal ending of the Bench-to-Bedside grant—in identifying and providing the best samples for us to test and to work on third-generation shorter peptides," Golding says.

For his part, Graham maintains that "this is Dr. Golding's project—and we're just trying to help." His role, he says, is mainly as a conduit to thousands of blood samples from the NIAID-funded HVTN.

Graham says that for the assay to have utility, it will eventually need to be licensed as a commercial detection kit and that its accuracy and sensitivity may help shape the content of future candidate HIV vaccines. "When Dr. Golding completes her testing and publishes her data, the scientific community and vaccine manufacturers will become aware of the need to design a vaccine to complement her assay—to avoid triggering a response detected by the new diagnostic test," he says, noting that candidate vaccines in VRC trials do not contain either the gp41 or Gag-p6 epitopes. ■

begun. By the time the vaccine is ready for testing in Zeichner's cohort, it will have been tested in more than 200 adults—first in uninfected and then in infected populations, Koup notes.

There was a six-month delay in the march toward the pediatric leg of the process when the DNA portion turned out to be "not as immunogenic as we would have liked" in the first study in uninfected adults, Koup recalls. "One component was re-engineered that component, and it looks as if we have a much more immunogenic DNA construct now."

Safety and immunogenicity are the endpoints in the studies of uninfected adults; immunogenicity and control of viral replication are the endpoints for infected adults.

Safety and tolerability are the fundamental endpoints of the phase 1 trial in children, with measure of the immune response to the vaccine a secondary objective, NCI's Carol Worrell, the study chair, emphasizes. She says there is reason to anticipate that children may have enhanced immune response to HIV antigens.

"We also have a strong interest in looking at the effect the immune response might have on viral reservoirs," Zeichner adds. A collaborator, Deborah Persaud of Johns Hopkins University in Baltimore, will be examining that issue once the trial begins.

While awaiting results from the adult trials, the teams have been characterizing existing humoral and cellular immune responses to HIV and pre-existing responses to the vector in their clinic patients who are candidates for the pediatric trial.

Zeichner expects to enroll 35 children who are currently doing well (sustained undetectable or low viral load and CD4 counts of at least 350) on a HAART regimen consisting of three agents from at least two drug classes.

Co-investigators in this project include Daniel Douek, Joe Casazza, and Barney Graham of the VRC, and Carol Worrell of NCI. ■

NIH Black Scientists Association

A Decade of Growth: Quality Outshines Quantity

by Myrna Zelaya-Quesada

It takes, I think, a strange combination of curiosity and just sheer madness to want to be a Ph.D. scientist these days," says Chad Womack, a senior research fellow in the Viral Pathogenesis Laboratory at the Vaccine Research Center. He proceeds, with humor, to list reasons why high school and college students in the United States might not be enthusiastic about a career in biomedical research.

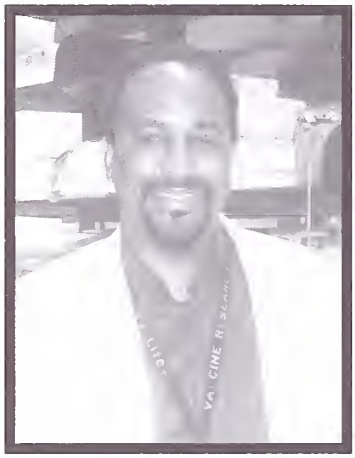
There's the time-in requirement to reach professional maturity—seven years to get a doctorate, another six or so in postgraduate training.

There's the monetary return after all the training—maybe half what could be earned if one had opted for medical or dental school and private practice.

There's no easy career path for anyone drawn to research, says Womack, whose own research interests have taken him to Morehouse School of Medicine and the Centers for Disease Control, both in Atlanta; the Harvard School of Public Health in Boston; and now the NIH.

And if the student is a member of an underrepresented minority, there's another layer of challenge—the relative scarcity of peers and mentors with familiar faces and backgrounds.

As president this year of the NIH Black Scientists Association (BSA), Womack hopes to advance more antidotes to this sense of aloneness.



Fran Pollner

Chad Womack, BSA president and senior research fellow at the VRC, is especially committed to identifying determinants of host-virus relationships that govern HIV disease in developing countries,, with a particular focus on the non-B subtypes of the virus. Additionally, along with Lauren Wood (NCI), he is co-recipient of a 2003 Bench to Bedside Award to study "The Use of 5-Fluorouracil (5-FU) in Combination with Antiretroviral Drugs as a Salvage Strategy to Overcome Drug Resistance in Heavily Treated HIV-Infected Pediatric Patients." (see p. 1)

The BSA—Yesterday and Today

Ten years ago, an NIH Committee on the Status of Intramural Minority Scientists issued a report and recommendations aimed at attracting and retaining minority scientists to all levels of involvement at NIH. The executive summary of the report was printed in the July 1994 issue of *The NIH Catalyst*, along with an editorial comment from Michael Gottesman, then acting deputy director for intramural research.

The report underscored the minuscule percentage of underrepresented minorities (Black, Hispanic, Native American, and Alaskan Native) in both the tenured and untenured ranks of NIH scientists—a little more than 2 percent of tenured scientists and a little more than 5 percent of nontenured scientists, as of October 1, 1992.

A decade later, the statistics are not dramatically different (see editorial, page 2), but the people counted in these numbers have access to a cohesive and convivial community of NIH minority scientists—an organization that meets regularly, conducts seminars and lecture series, sponsors a scholarship program for minority Washington, D.C., high school students, runs a speakers bureau, and strengthens the personal and professional connections among its members.

That organization—the BSA—was born in the fall of 1994, on the heels of the release of the status report on NIH minority scientists. Initially called the Minority Scientists Association, the name was changed the following year to represent more accurately the people who were actually working in the organization.

A Home Base

The BSA is a remedy against isolation, "the hub of a community," says Womack.

"It's a place where you can let your hair down and just relax, where you can talk about science, talk about research, but also talk about other subjects that might be on your mind," Womack says. That the NIH research program houses a vibrant scientific community of all races, colors, and backgrounds is a plus. But in an area as large and productive as the NIH campus, it's easy to get lost in your own lab, he observes, and never run into other people with whom you may have much in common.

The name notwithstanding, the BSA's door has always been open to all members of the NIH research community, regardless of ethnic background. "I want to stress that," says Womack. "Anyone [who supports] the goals of the BSA is welcome to join" (See "BSA Objectives").

On the Agenda

Indeed, among the organization's current objectives is expanding the membership. In addition to a general welcome to all who share similar commitments, overtures are being made to senior administrators who have not been involved in the program and to African-American scientists on the extramural side of NIH.

Additionally, BSA members are encouraged to invite friends and colleagues from their respective institutes to BSA meetings and events. Such outreach may involve others who work in NIH groups that are interested in advancing a diversity of issues while maintaining a rigorous scientific workforce. Scientific rigor, Womack emphasizes,

BSA Objectives

The BSA website—**<http://bsa.od.nih.gov/>**—notes that its members *have come together to get to know each other as people and as professionals, to promote our individual and collective professional advancement, and to advocate various health and scientific issues of importance to underrepresented minority communities in general and to the Black community in particular. . . . We provide information, contacts, and a sounding board on issues of importance to minority scientists, physicians, technologists, and patients. Of particular interest at NIH are issues concerning the recruitment, development, recognition, and promotion of Black scientists and clinicians, as well as the selection and care of Black patients and research subjects.* ■

The Diggs Legacy

Members of the NIH Black Scientists Association cannot talk about the organization's beginnings and continuing spirit without acknowledging the influence of John Diggs, former deputy director for extramural research who left NIH in 1993 but kept in close contact with his former colleagues and the founding members of the BSA.

The first annual John W. Diggs Memorial Lecture was held in July of 1995, two months after Diggs died, and continues as an intellectual highlight of the BSA's scientific programs and a tribute to a revered member of the Black scientist community. ■

Some BSA Profiles and Reflections

by Myrna Zelaya-Quesada

Felicia Eason Forbes, a postdoctoral fellow in the lab of Robert Nussbaum at the Genetic Disease Research Branch, NHGRI, is a member of the BSA's Cheryl Torrence-Campbell (CTC) Scholarship Committee. Eason Forbes' research focuses on identifying genetic mutations in Lowe oculocerebrorenal syndrome, a rare X-linked disease characterized by mental retardation, seizures, congenital cataracts, and renal Fanconi syndrome. "I enjoy the day-to-day challenges of working on a project that will hopefully add to the scientific knowledge base. I also enjoy working with the brightest minds in a wonderful environment here at NIH," Eason Forbes says.

Fran Pollner

Felicia Eason Forbes and nine-month-old Nia

On the BSA: Eason Forbes mentors the high-school recipients of the CTC Scholarship and expects that the mentoring program will branch out to encourage more minorities at all levels of training to enter the field of research. Her enthusiasm for mentoring was fueled by her appreciation of the senior scientists and postdocs who have mentored her. "They helped mold me into a better person, and I am grateful."

George Redmond, currently BSA vice-president, is a clinical informatics expert at the NCI Cancer Therapy Evaluation Program and an advisor to the NCI Center for Bioinformatics. The BSA's first president, Redmond was critical in developing the organization's mission and strategic objectives for addressing the concerns and needs of the minority scientist community, particularly African-Americans.

Myrna Zelaya-Quesada

George Redmond

On the BSA: "I have established lifelong relationships with people that directly contribute to public health and biomedical research. These relationships have exposed me to an ever-expanding environment of innovation in science and [have shown me] how far-reaching is the societal benefit of biomedical research . . . . [they've also] allowed me to gain insight into the wonders and beauty of life."

Roland Owens is a senior investigator/research biologist in the Molecular Biology Section of the Laboratory of Molecular and Cellular Biology, NIDDK. One of the co-founders of the BSA, Owens has been its president, vice-president, secretary, co-chair of the Speaker's Bureau, and chair of the Career Enhancement Committee. At the bench, his group studies adeno-associated viruses and their development as gene therapy vectors in the treatment of diabetes and other diseases.

Roland Owens

On the BSA: "The BSA enables us to network with other Black scientists and to help [each other] thrive in science. Through the network, I was able to recruit a postdoctoral fellow. He published two first-author papers and two middle-author papers with me and is now a project manager with a major pharmaceutical company. My work with the BSA's Speaker's Bureau allowed me to meet many of the best Black biomedical researchers in the world, many of whom I would not have met through any other mechanism. It has also allowed me to have many Black scientist friends, something I never experienced before I joined this organization."

Lauren Wood is a clinical PI for the Pediatric HIV Working Group of the HIV & AIDS Malignancy Branch, NCI, and co-director of the NCI Pediatric Outpatient Clinic. Along with Chad Womack (NIAID), Wood is co-recipient of a 2003 Bench-to Bedside Award on "Use of 5-Fluorouracil (5-FU) in Combination with Antiretroviral Drugs as a Salvage Strategy to Overcome Drug Resistance in Heavily Treated HIV-Infected Pediatric Patients (see p. 1)." Having cared for many of her patients since they were toddlers, she says, it is especially rewarding to see their maturation into adolescents and young adults due to advances in treatment. "Adolescents with HIV have many unique issues, although they also face challenges similar to other teens with chronic illness such as asthma or diabetes."

Fran Pollner

Lauren Wood

On the BSA: "There is a real void in terms of diversity in the NIH community at the senior scientific level. I think that people need to understand that diversification of the workforce is not only necessary, it is what actually would maximize the NIH in terms of its addressing its mission to impact the health of the American public."

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has always been a BSA priority.

The organization is also undertaking a comprehensive survey of Black scientists on campus. Starting with its own membership, the organization will branch out and collect data on the numbers of African-Americans working in various capacities at the tenured, tenure-track, postgraduate, graduate, and undergraduate levels across NIH.

Another initiative builds on one of the BSA's most cherished projects. Established in 1999, the Cheryl Torrence-Campbell Scholarship is offered annually to minority college-bound seniors in Washington, D.C., high schools who are pursuing a science-related major—one means to encourage that "strange combination of curiosity and just sheer madness" needed to pursue scientific research.

Accompanying the scholarship is a mentor, gratis, to guide the student through whatever educational and professional challenges may arise. The BSA intends to expand the scholarship program this year to include college and graduate students in need of support. Womack would like to see the program extend across the country. ■

Summer Poster Day: An August Showing along the "Road to Discovery"

by Aarthi Ashok and Fran Pollner

Hailing from high schools, colleges, and graduate schools, this summer's NIH trainees set a record for participation in Student Poster Day—530 students presented 515 posters across the vast spectrum of research interests of the 25 institutes and centers that have been their workplaces during their "summer break." We briefly report on less than one percent.

Inhibiting HIV with Alloimmunized Lymphocytes

Rebecca Burke, Brown University, Providence, R.I., and Christina Nelson Perez, Case Western Reserve University School of Medicine, Cleveland. ***Alloimmunization as a Strategy for HIV Therapy***
Preceptors: Chad Womack, Viral Pathogenesis Laboratory, NIAID-VRC, and Lauren Wood, HIV & AIDS Malignancy Branch, NCI

Previous work by NCI's Gene Shearer demonstrated that stimulation by foreign lymphocytes generates an alloresponse in ordinary lymphocytes that results in their ability to inhibit HIV replication in vitro.

The current study—comprising three experiments—seeks to characterize the alloresponse and identify the source of anti-HIV activity.

First, the team isolated CD8+ T-cells and stimulated them with foreign B-cells to establish whether the activated CD8 cells would inhibit HIV replication in the presence of HIV+ CD4 cells. This experiment, Nelson Perez noted, proved inconclusive because both the experimental and the control cultures came back negative for HIV.

The second experiment examined the surface markers of the CD8 cells before and after alloactivation. FACS analysis showed that CD27 and, to a lesser extent, CD45RA increased post-alloactivation, while CCR7 and HLA-DR decreased.

Fran Pollner

Rebecca Burke (left) and Christina Nelson Perez

The third experiment, soon to be undertaken, will expose HIV-infected cells to each of these CD8 subpopulations separately to see to what extent each factor contributes to HIV inhibition.

The ability eventually to identify correlates of alloimmunity with CD8 T-cell effector function may lead to the design of immunotherapies for transplant, cancer, and HIV patients.

Nelson Perez, who just graduated from medical school, says she's been "bitten by the HIV research bug." She's interested in pediatrics and public health. Burke, now applying to medical school, is drawn to pediatrics.

—Fran Pollner

When a Pathway Meets a Pathway

Vishal Sidhar, New York Medical College. ***Characterization of a Clathrin-Independent Pathway in a Variety of Cell Types***
Preceptors: Julie Donaldson and Roberto Weigert, Laboratory of Cell Biology, NHLBI


Fran Pollner

Vishal Sidhar

The transport of proteins and lipids to and from the plasma membrane is achieved through different cellular trafficking systems that are critical for interactions of all cells with their environment and hence for cell survival.

These transport pathways can be broadly classified as either clathrin-dependent or clathrin-independent, based on whether or not the transport vesicles are coated with the protein clathrin.

The clathrin-dependent endocytic pathway has been extensively studied in many cell types, whereas studies describing the clathrin-independent pathway are just emerging.

In HeLa cells, previous studies showed that these two different pathways can function independently of each other to transport distinct cargo but converge at the early endosomes compartment and that the GTPase Rab22a is involved in the recycling of the clathrin-independent cargo back to the membrane.

Sidhar sought to understand whether the convergence of these two pathways and the GTPases involved in the regulation of the clathrin-independent pathway are conserved in cell types other than the HeLa cell.

Using transferrin as a marker for the clathrin-dependent pathway and MHC class I molecules as a marker for the clathrin-independent pathway, Sidhar examined these pathways in human, canine, and monkey cell types by confocal microscopy.

There was very little overlap observed between transferrin and MHC I molecules in all cell types examined when fluorescently tagged forms of these markers were added to cells for short time periods, indicating that each marker was internalized by a distinct pathway.

However, not all the cell types showed significant overlap of these markers at later times, suggesting that these pathways may not converge in all cell types as was seen in the HeLa cell.

MHC I molecules were present in unique membrane tubules that extended out to the plasma membrane in all these cell types. Sidhar observed that the Rab22a GTPase was present in membrane tubules reminiscent of the MHC I localization pattern.

He further noted that when a constitutively active form of Rab22a (Rab22a-Q64L) was overexpressed in these cells, there was an increase in the number of long tubules, while overexpression of an inactive form of Rab22a (S19N) led to an absence of tubules.

This result suggested that Rab22a did indeed control the recycling pathway in these cell types similar to HeLa cells; it also implicated Rab22a function in the recycling of material internalized through the clathrin-independent pathway.

Sidhar hopes these preliminary findings will lead the way for future studies that will characterize the cellular machinery required for the clathrin-independent pathway to function in all cell types.

—Aarthi Ashok

LOSS OF INHIBITION?

Eric A. Brown, Physician Scientist Training Program, George Washington Carver High School of Engineering and Science, Philadelphia. ***Mutation of the Helicase Domain of Adeno-associated Virus Rep Proteins and Its Impact on Rep-mediated Inhibition of Cell Division***

Preceptor: Roland Owens, Laboratory of Molecular and Cellular Biology, NIDDK

Adeno-associated virus, a nonpathogenic human parvovirus that is being evaluated for its utility as a gene therapy vector, encodes the Rep 78 protein, which plays a role in the regulation of viral replication, integration, and gene expression. The helicase function of Rep 78 may be important for Rep 78's abilities to inhibit cell division and regulate oncogenic transformation.

Recent studies from the labs of Robert Kotin at NHLBI and others have shown that mutation of lysine at the 340 position (K340) in the helicase domain eliminated this inhibitory effect on cell division. Brown set about to test the hypothesis that other mutations in the helicase domain would also interfere with the inhibitory effect.

Fran Pollner

Eric Brown

To this end, he designed a plasmid construct containing the Rep 78 open reading frame (ORF) under the control of the CMV promoter and carrying the neomycin resistance gene (*neo*).

Other constructs carried various mutations in the Rep 78 helicase domain or the *neo* gene alone as a positive control. All constructs were transfected into HeLa cells.

To the surprise of Brown and his colleagues, cells transfected with the normal Rep 78 ORF grew more efficiently than the *neo*-transfected controls—contrary to the findings of Kotin and others.

Brown speculates that differences in construct design might explain the discrepancy. "We believe that the integration of our construct into chromosome 19 may occur in such a way that the CMV promoter is lost, leading to enhanced expression of the *neo* gene but loss of Rep 78 protein expression," he says.

He hopes to examine the integration of both the *neo* and *rep* genes into the chromosome 19 locus to better understand these interesting findings. He's also contemplating a career as a physician-scientist.

—Aarthi Ashok

HEIGHT AND PROSTATE CANCER

Fran Pollner

Jacqueline Sequoia

Jacqueline Sequoia, San Diego State University Graduate School of Public Health. ***A Prospective Investigation of Height and Prostate Cancer Risk in Male Smokers***

Preceptors: Demetrius Albanes and Margaret Wright, Nutritional Epidemiology Branch, NCI

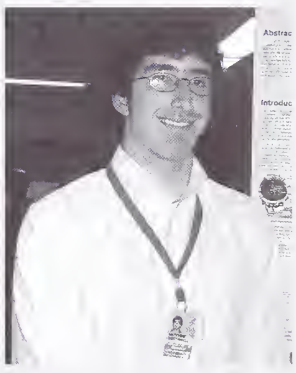
Prostate cancer is the most commonly diagnosed malignancy and the second leading cause of cancer-related deaths in men in the United States. Increased adult height, an indication of early nutrition and genetic predisposition, has been positively associated with prostate cancer risk in several studies, although somewhat inconsistently. To address some of the discrepancies, Sequoia and her colleagues studied the association of height and prostate cancer incidence in 29,119 Finnish male smokers, aged 50 to 69 years, enrolled in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study.

During up to 17 years of follow-up, 1,346 incident prostate cancers were identified. Results indicated that the taller men had up to 30 percent higher risk of prostate cancer, particularly of advanced-stage disease, than did shorter men.

Sequoia and her colleagues suggest that exposure to higher levels of growth hormone, insulin-like growth factors, androgens, and/or nutrition during puberty may increase both adult height and the risk of prostate cancer.

—Aarthi Ashok

INHIBITING HIV VIA YEAST-BORNE PEPTIDE



Fran Pollner

Matthew McConnell

Matthew McConnell, Amherst College. ***Secretion of HIV-Inhibitory Peptides by Commensal Yeast.***

Preceptors: Dean Hamer and Kenneth Henry, Laboratory of Biochemistry, NCI-CCR

If the yeast that lives in the mucosal compartments of the human body could passively secrete HIV inhibitors, that would be an ounce of AIDS prevention more reliable than condom usage.

Such is the driving rationale behind a study to establish a yeast expression and secretion system for C-51, a peptide that inhibits the fusion step of HIV infection. This, McConnell says, is the "very first step" on the road to clinical manipulation of yeast that live commensally in the human body, especially in the gastrointestinal tract, where much of the early infection and viral replication of HIV take place.

The team succeeded in integrating C-51 into a yeast genome and inducing its expression and secretion; the peptide demonstrated active inhibition of both CCR5- and CXCR4-tropic HIV strains. Moreover, there was evidence that the secreted peptide was glycosylated, which could enhance stability, McConnell adds.

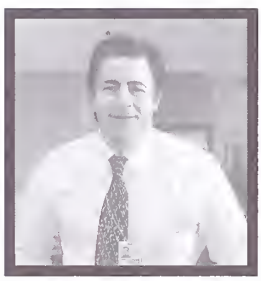
The team's next step is to determine whether glycosylation improves stability and affinity of C-51 in vitro and in vivo; McConnell's next step is to begin his third year of college and his work toward a degree in chemistry. Beyond that lie M.D. and Ph.D. degrees.

—Fran Pollner

People

Recently Tenured

Mark Gladwin *received his M.D. from the University of Miami Honors Program in Medical Education in 1991. After completing his internship and chief residency at the Oregon Health Sciences University in Portland, Ore., he joined the NIH in 1995 as a critical care fellow in the Clinical Center. After a one-year clinical fellowship in pulmonary medicine at the University of Washington in Seattle, he returned for a research fellowship at the Critical Care Medicine Department, CC, under the mentorship of James Shelhamer, Frederick Ognibene, Alan Schechter, and Richard Cannon. He is currently head of the Vascular Therapeutics Section, a new section within the Cardiovascular Branch, NHLBI.*



Fran Pollner

Mark Gladwin

The clinical research activities of the Vascular Therapeutics Section are linked to the CC Critical Care Medicine Department. This collaborative effort intends to develop a new scientific research program focused on four major lines of research, each containing a strong and smooth interaction between bench and bedside investigations.

The first major area of my section's investigation focuses on the biochemistry of nitric oxide (NO), nitrite, and hemoglobin in blood and the role of such chemistry in physiology and pathophysiology. These studies span basic chemistry and development of methods, biomarkers for endothelial function, and clinical protocols for nitrite and NO therapeutics.

A second major area of research evaluates endothelial dysfunction in sickle cell disease. This includes basic studies of the dysregulation of NO-dependent blood flow and NO bioavailability in sickle cell disease and extends to clinical trials of pharmacotherapy for endothelial dysfunction in affected patients.

The third area of active research explores the emerging syndrome of hemolysis-associated pulmonary hypertension common to sickle cell disease, thalassemia, and most chronic hereditary or acquired hemolytic anemias. These investigations will evaluate the role of NO scavenging by plasma hemoglobin in the development of endothelial dysfunction, adhesion molecule upregulation, endothelial permeability, and oxidant stress.

A final area of active investigation covers global transcriptional analysis in human vasculopathy, with the focused development of assays to amplify key expressed genes in target tissues (endothelial cells, platelets, and monocytes) in patients with sickle cell anemia, pulmonary hypertension, and endothelial dysfunction syndromes. We are also evaluating the protective effects of the heme-oxygenase system and heme-induced catalytic antioxidant systems in these diseases.

Over the past six years, our research in these areas has led to four important scientific discoveries, 56 published manuscripts, 18 pending or approved protocols, and 462 patient enrollments.

The four scientific discoveries are

- The characterization of a novel mechanism-of-disease paradigm, namely, hemolysis-associated endothelial dysfunction (Reiter, et al. *Nature* 2003)
- The mechanistic, clinical, and epidemiological description of a human disease syndrome, namely, hemolysis-associated pulmonary hypertension (Gladwin, et al. *NEJM* 2004)
- The discovery that the nitrite anion is a circulating storage pool for NO (Gladwin, et al. *PNAS* 2002)
- The discovery of a novel physiological function for hemoglobin as an electronically and allosterically regulated nitrite reductase (Cosby, et al. *Nature Medicine* 2003)

Fran Pollner

Markus Heilig

Markus Heilig *received his M.D. and Ph.D. in psychiatry from Lund University, Sweden, in 1986 and 1989, respectively. After completing postdoctoral research at Scripps Research Institute in La Jolla, Calif., and a clinical fellowship at Göteborg University in Sweden, he became director of the addiction medicine department at the Karolinska Institute in Stockholm. He was chief of research and development in the psychiatry division of the Clinical Neurosciences Department at Karolinska before joining NIAAA in 2004. He is chief of the Laboratory of Clinical Studies and clinical director of the Division of Intramural Clinical and Biological Research, NIAAA.*

One day you have life all worked out, from who's picking up what kid where, to automatic notification when a postdoc posts a revised paper on the server. One flight later, nothing is in place, and you can't get a phone without a $500 deposit. I've moved before, but, oh, is it different to pack up the life of a single postdoc vs handling the transition for a family of six and a research group of 10.

So at 4 in the morning I have to remind myself why. Because the U.S. makes an investment in biomedical research that on an average gives a group in the neurosciences sevenfold larger resources than a comparable group at the Karolinska, my former research home. Because the NIH community therefore has become an environment to be admired by all the Karolinskas and Cambridges of the world. And because the alcohol institute is in the process of developing an agenda combining great science with clinical relevance, which appeals to me as a clinician.

What got me tenured? They don't tell you, do they? And I find it embarrassing to boast any accomplishments. My interest is in motivation and emotion, nowadays primarily as they relate to alcohol and drug abuse. I'm a clinical psychiatrist, saw the last patient three weeks ago [mid-July], and still coordinate a government-sponsored clinical trial for pharmacological treatment of heroin addiction in Sweden.

But for the last 15 years, I've also used preclinical models to identify potential new treatment targets for addiction, anxiety, and depression. Like most, I started out testing my own favorite candidates. So if you want to discuss neuropeptide systems like NPY, CRF, and tachykinins, stop by and let's have a cup of coffee.

But recently, we've gone to the more humbling open-ended strategies, to discover targets we wouldn't have been able to hypothesize. We model the course of neuroadaptive processes in the brain as it undergoes repeated cycles of alcohol intoxication and withdrawal, and we use DNA arrays to identify new targets. So far, the list of hits includes cannabinoid receptors and several signal-

ing pathways that seem quite promising. We've been fortunate enough to join a core array facility between NHGRI, NINDS, NIMH, and now NIAAA (thank you, Eric Green of NHGRI for working it out). So if you're interested in that as a strategy, or any of those targets, come by for a second cup.

But of course it doesn't stop there. If it did, I could be at any well-funded pharmacology department. The unique potential of the intramural program, and the NIAAA laboratory of clinical studies in our case, is to take whatever comes out from the rat and mouse models and go on. Where else could I speak to a world-class primatologist, Dee Higley, and do studies that model craving and decision-making in ways that are just too complex for rodents? Where else discuss with a first-class imaging expert, Dan Hommer, how to find the regional brain metabolism "signature" of the relevant clinical states and see how clinically effective drugs modify it? And finally and most importantly, where else take whatever looks interesting after this set of translational filters, and actually test it for clinical efficacy, in-house?

Maybe it is this kind of integrative capacity, from molecule to patient, rather than a specific paper the tenure committee liked? I'd like to think of it that way. And once I figure out how to get that phone, and how to fill out all the forms (23 at present count), I'll start enjoying the fantastic opportunities of this great place. If we don't come up with some clinically useful treatments within the next five years, I'll have no excuses.

Konrad Noben-Trauth

Konrad Noben-Trauth *obtained his diploma in Biology from University of Heidelberg in Germany in 1990. He was awarded a Ph.D. in Molecular Biology from University of Freiburg in Germany in 1994. In his thesis he studied the murine* myb *gene family of transcription factors in the laboratory of Karl-Heinz Klempnauer at the Max-Planck-Institute for Immunobiology in Freiburg. He performed postdoctoral studies at The Jackson Laboratory, Bar Harbor, Me., in the lab of Patsy Nishina and Jurgen Naggert from 1994–1997, investigating the genetics of sensorineural defects in mice. He joined NIDCD in 1997 and currently heads the Section on Neurogenetics.*

Hearing is the perception, transmission, and interpretation of acoustic stimuli. It is a multistep process that involves the mechanical deflection of stereocilia hair bundles on sensory hair cells in the organ of Corti, opening of mechanically gated transducer channels, and transmission of the electrical stimuli to the eighth cranial nerve for further processing in the central nervous system.

My lab is interested in the molecular factors and mechanisms that underlie the initial steps of this pathway. We apply a positional cloning strategy, using classical mouse deafness mutants (deafwaddler, waltzer, varitint-waddler, Jackson circler) and common inbred strains (C57BL/6J, DBA/2J), that segregates monogenic and polygenic sensorineural hearing loss. This forward genetic approach is ideal for dissecting molecular pathways in the organ of Corti because there are many mouse mutations with defects in the cochlea. In addition, deaf mice often replicate human hereditary hearing loss and thus can be used to study the cellular and molecular underpinnings of human deafness.

The varitint-waddler (*Va*) mouse carries a semi-dominant mutation causing early-onset hearing loss, vestibular defects, pigmentation abnormalities, and perinatal lethality. Hearing loss is preceded by the disruption of the organizational structure of the stereocilia hair bundle during late embryonic development, subsequently leading to hair cell degeneration.

We identified two new members of the Mucolipin gene family in the critical interval and identified causative missense mutations in Mucolipin-3 (*Mcoln3*). *Mcoln3* encodes a TRP ion channel, which localizes to vesicles and the plasma membrane of stereocilia, leading us to hypothesize that Mucolipin 3 is involved in mechanotransduction.

Deafwaddler (*dfw*) is a recessive mutation that leads to congenital deafness and locomotor abnormalities. In collaboration with Bruce Tempel (University of Washington in Seattle), we showed that the plasma membrane calcium pump PMCA2 (*Atp2b2*) is essential for balancing Ca^{2+} levels in stereocilia. Ca^{2+} plays an important role during the fast and slow adaptation process of the mechanotransduction complex.

Our work on the deafwaddler mutation showed that its recessive inheritance is tightly controlled and modified by the genetic background: On the CAST/Ei strain, heterozygotes exhibit a normal phenotype, whereas on the BALB/cByJ background, *+/dfw* mice are deaf. We mapped this modifier locus (*mdfw*) close to the waltzer mutation.

Waltzer mice show erratic circling behavior and are deaf from birth. We cloned a new type of cadherin, cadherin 23, encoding a 3,354–amino-acid single-pass transmembrane protein with 27 extracellular cadherin domains. Based upon its predicted function and the disorganized stereocilia bundle in waltzer mutants, we proposed cadherin 23 as a component of the inter stereocilia links that structure the hair bundle and connect the individual stereocilia.

In collaboration with Christian Kubisch, University of Bonn in Germany, we also demonstrated that the human homolog, *CDH23*, underlies Usher syndrome type 1D, a recessive disorder characterized by deafness, blindness, and vestibular deficits.

Recent work from my lab showed that a functional single-nucleotide polymorphism (SNP) in *Cdh23* explains the *mdfw* modifier effect. The silent single-nucleotide change occurs at the last position in exon 7 of *Cdh23* and alters splicing, generating a protein with diminished function.

We also showed a near-perfect correlation between this hypomorphic *Cdh23* allele and age-related hearing loss (AHL): Of 31 inbred strains classified with AHL, 27 carry the hypomorphic allele, and of 25 normal-hearing strains, 22 segregate the wildtype variant. We concluded that the polygenic hearing loss observed in many common inbred strains—such as C57BL/6J, 129/Sv, and DBA/2J—is largely caused by this SNP in *Cdh23*.

We plan to study additional complex inheritance models, especially those found in outbred populations. We are interested in the molecular function of *Mcoln3* and *Cdh23* and their role in the transduction current and stereocilia maturation. We plan to expand our genetic studies into human populations with emphasis on the susceptibility to noise-induced hearing loss. In the more distant future, we hope to use some of the hearing loss strains as models for stem-cell–based therapeutic approaches.

Recently Tenured

Weidong Wang *received his Ph.D. from the University of California, Los Angeles, in 1991. He performed his postdoctoral training at Stanford University in Stanford, Calif. He has been chief of the Transcription and Remodeling Unit, Laboratory of Genetics, NIA, since his arrival at NIH in 1997.*

Weidong Wang

Multiprotein complexes have been implicated in the regulation or modulation of many cellular processes. Usually, a cellular protein is not present on its own. Instead, it will often be present in several complexes, with each complex performing a unique function. Thus, the biological functions of a given protein can be fully understood only when the consequences of its association in complexes are defined.

Our unit has used a biochemical approach to defining targeted complexes, starting with the development of a highly efficient immunopurification protocol to isolate the endogenous complexes from mammalian nuclear extracts in highly purified form. We have focused on studies of two families of multiprotein complexes involved in gene expression and genome stability, in two corresponding projects:

■ **Project I. Chromatin-remodeling complexes that participate in gene regulation**

■ **Project II. Nuclear complexes involved in genome instability syndromes**

In the eukaryotic nucleus, the chromatin structures that store genetic information tend to render the DNA inaccessible to metabolizing enzymes. This repressive chromatin structure must be remodeled to allow transcription and other metabolic reactions to occur. Chromatin-remodeling complexes play key roles in the remodeling process, which is critical for multiple cellular functions, including transcription, replication, repair, chromatin assembly, and chromosome condensation. In addition, multiple human diseases, including several types of cancer, are caused by mutations in remodeling complexes; and aging in several lower species can be modulated by alterations in remodeling enzymes.

In Project I, we purified several complexes of the SWI/SNF family, identified and cloned their subunits, and demonstrated that these complexes mediate transcriptional activation for specific gene regulators. We showed that one of these complexes contains a fusion partner for mixed-lineage leukemia (MLL) protein, which is a common target for chromosomal translocation in human acute leukemia. Our work implicates human SWI/SNF complexes in the etiology of leukemia.

In another study, we identified a novel complex, called NURD, and showed that it is involved in repression of gene expression. An unusual feature of this complex is that it contains two seemingly opposite chromatin-remodeling activities. One is removal of a chemical modification of chromatin. This action is often involved in gene repression. NURD's other activity is energy-dependent chromatin disruption, which, at the time of our study, was associated only with gene activation. But our data suggest that energy-dependent chromatin-disruption can also participate in gene repression by helping repressors to gain access to their targets in chromatin.

We recently identified a complex involved in human ATR-X syndrome. Patients with ATR-X syndrome have severe mental retardation and α-thalassemia (lower level of α-globin in blood). We demonstrated that the defective protein defective in this disease forms a new chromatin-remodeling complex with a regulator of gene expression. Defects in this disease may thus result from inappropriate expression of genes controlled by this complex.

In Project II, we purified several multiprotein complexes involved in human genomic instability diseases, including Fanconi anemia, Bloom syndrome, and Rothmund-Thomson syndrome. Among them, the purification of the Fanconi anemia core complex has led to novel insights into the disease mechanism, including the discovery of four new genes, whose mutations may cause Fanconi anemia (we have confirmed two of these and are accumulating evidence for the other two).

Recessively inherited, Fanconi anemia can include congenital defects, bone marrow failure, genomic instability, and cancer susceptibility. Patients have been classified into 11 complementation groups, with each group carrying genetic mutations in the same gene.

Recently, studies of this rare disease have attracted widespread attention because one of the Fanconi genes, *FANCD1*, has been shown to be identical to the breast cancer susceptibility gene *BRCA2*. It is now believed that Fanconi and breast cancer proteins may function in the same pathway during DNA damage response. However, the mechanism underlying this pathway has been poorly understood, because most known Fanconi proteins lack recognizable structure motifs and an identifiable biochemical activity.

We have purified a nine-subunit Fanconi protein complex and found that it contains not only five known Fanconi proteins, but also four other proteins. We demonstrated that two of the new proteins are also Fanconi proteins, and their corresponding genes are mutated in Fanconi patients of two different complementation groups. Our current data suggest that the other two new proteins also have important biological function for this complex, and their genes are candidates as new Fanconi genes.

We also found a structural motif. One of the new Fanconi proteins has a ubiquitin ligase motif and displays this activity in test tubes. Ubiquitin is a small protein molecule that can be covalently linked to other proteins to initiate protein degradation, translocation, and other biological processes.

It is known that one of the Fanconi proteins, FANCD2, is subject to ubiquitination in response to DNA damage, and this ubiquitination reaction is a key step in the Fanconi protein pathway. The underlying ubiquitin ligase for this reaction has been unknown for some time.

We demonstrated that the ubiquitin ligase identified in our study is most likely the ligase for this reaction, because cells derived from a Fanconi patient with mutation in this gene have complete absence of FANCD2 ubiquitination. Moreover, putting this ligase back into the patient's cells can correct the defective ubiquitination reaction—at least in vitro.

All our work has been greatly benefited from collaborations with other groups within and outside NIH. We are continuing these collaborations to uncover new disease genes and to better understand the mechanisms of transcription and genome maintenance. ■

The Food Offense: A Technique for Stress Reduction in the Laboratory

by Howard Young
Laboratory of Experimental Immunology
NCI-FCRDC

Maintaining positive interactions between laboratory personnel is a crucial aspect of managing a laboratory.

As laboratories become more crowded, personality conflicts invariably arise and when they do, the entire laboratory can suffer from the increased stress and tension that may occur.

I report here a novel and unique method for reducing stress in the laboratory. This method, termed a food offense, has been used by my laboratory for many years and has proven successful in defusing the occasional stressful laboratory incident.

I first published "Food Offense" in 1993 in a now-defunct technology newsletter and again in a newsletter of which I am the editor. It has been sighted taped to a wall in a laboratory in Rome and paraphrased in a business section article of a major metropolitan newspaper. Here it is updated for the 21st century.

The Offense

A food offense is defined as a situation in which the actions of one member of the laboratory lead to the disruption of the work of other members of the laboratory. While there may be a strong debate regarding whether a specific act is a food offense, a majority vote in the lab is sufficient to declare a food offense. Examples of food offenses are as follows:

1. Using up a common lab reagent (such as gel electrophoresis buffer) and not remaking it before the next person needs it

2. Leaving common equipment (such as a tissue culture hood) so messy that the next user must clean it before it can be used

3. Using isotope and not recording its removal—so that the next user winds up not having as much as expected

4. Stripping a blot for someone, but forgetting about it—so that the blot burns after the buffer boils away (this actually happened in the older days when people actually did blots)

5. Providing the wrong restriction map with any plasmid (or not providing any restriction map at all)

6. Tearing a journal article out of a journal before anyone else has read it

7. Providing the wrong control sample for the latest microarray experiment

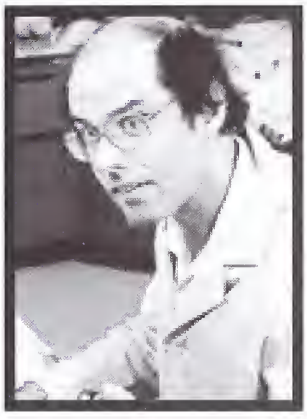
8. Scheduling a lab meeting but forgetting to show up despite the fact everyone else managed to remember

9. Neglecting to tell the lab that the cell line you work with is contaminated with Mycoplasma

10. Starting a gel for someone but plugging the electrodes in backwards

11.. Forgetting to turn off a gel for someone

12. Spilling radioisotope and not cleaning it up or telling anyone that a spill occurred (extreme)



Howard Young

13. Leaving a big, heavy rotor in a centrifuge when you know the next person to use it is 5' 2" tall, weighs 90 pounds, and needs the smaller rotor

14. Breaking any piece of equipment and not telling anyone

15. Leaving the flow cytometer on all night

16. Not showing up for two days and never telling anyone that you were going to be away

17. Holding a manuscript that you promised to review well beyond its due date

18. Playing really bad music on the lab CD player (this is often subject to a major debate)

19. Falling asleep in a lab meeting when a member of your group is presenting data (people over 55 may be exempt from this rule)

20. Borrowing a reagent from another lab and either never replacing it or replacing it six months later

The Offering

When a food offense is committed and the individual is identified, the individual is given two options:

Option #1. Start looking for another job.

Option #2. Bring in food for the lab.

Because choice #2 is the preferred response, the type of food that satisfies a food offense is somewhat restricted. The rules are as follows:

1. Homemade food, preferably containing chocolate, is desirable but not absolutely required.

2. Certain foods, such as Vegemite from Australia or gefilte fish, do not satisfy a food offense.

3. Healthy foods might qualify but only if they taste like something fattening.

4. Trying a recipe for the first time should generally be avoided unless you are absolutely sure it is wonderful.

And Furthermore

There are a few additional rules that apply to a food offense.

1. New students are exempt for the first two weeks in the lab because they are generally expected to mess something up.

2. Food offenses only apply to incidents in which other lab members are affected. If you use up the isotope, but no one else in the lab uses it, that is not a food offense.

3. No one is exempt from food offenses, including the head of the lab.

4. Poverty cannot be claimed as a reason to avoid providing food. A dozen doughnuts will not break anyone.

5. The person who commits the food offense is allowed to partake in the eating. In fact, one might well be wary of food that is avoided by the individual who provided it.

6. One cannot prepay food offenses. However any food brought for the lab is always welcome.

7. If the food offense payment is really bad, the individual committing the food offense should be required to try again.

Finally, if your laboratory has any individuals who commit food offenses but absolutely refuse to cooperate, it might be well to invoke option #1.

Anyone who cares so little about the other members of a laboratory and constantly creates stressful situations is probably more trouble than they are worth and might be better off somewhere else.

I wish to acknowledge all the past and present members of my laboratory who have cooperated fully with me in reducing stress and tension in the lab.

However, I cannot imagine I could ever have committed any of the food offenses with which I have been charged. ■

CATALYTIC REACTIONS?

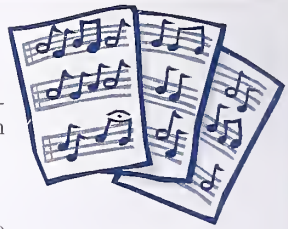
If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation that scientists might appreciate that would be fit to print in the space to the right, why not **send it to us via e-mail: catalyst@nih.gov>; fax:402-4303; or mail: Building 2, Room 2E26.**

Also, we welcome "letters to the editor" for publication and your reactions to anything on the *Catalyst* pages.

In Future Issues...

- IRP Research Roundup
- Research Festival/ Job Search
- Teams for the Road

Kids' Catalyst—Tone Trek



Welcome back! We hope that your summer was fun and even educational. Ready to start playing? Here are some experiments that start with sounds and end with . . . . well, that's up to you!

Clanging Glasses

You'll need: ■ One set of three glasses (real glass—plastic doesn't work so well—wonder why?) ■ Another set of three glasses of similar shape, but different size ■ Water ■ A pencil

Fill the first glass to the top with water. Pour the water from the first glass into the second glass until they're even. Then take the second glass and pour water into the third glass to make them even. Take one of the 1/4-full glasses and fill it all the way up. Now you have three glasses—one is full, one 1/2 full, one 1/4 full.

Now take a pencil and tap the side of the glasses. You don't need a piano to tell that they all sound different. (If you have a music teacher around, ask them to write the notes down on the staff.)

Now it gets really interesting. Use the same method to fill the next set of glasses. They're not the same glasses, but they still follow the same pattern. You'll find that the difference between the first and second glasses is the same as the second and third. Do you think this will work for glasses that have a completely different shape? Give it a try. Do you think the difference will be the same or less with four glasses filled in 1/4-glass increments? What about 12?

Singing Coins (in Balloon)

You'll need: ■ A balloon ■ A penny, a nickel, a dime, and a quarter

This one is really fun! Blow up your balloon, choose a coin and place it *inside* the balloon, and twirl. Pretty strange sound, huh? Try whirling at different speeds, and write down how the sound changes when it's going fast or slow. Try this with the other coins, too. Does a quarter sound different from the dime? What about how inflated the balloon is? Does that change the tone?

Whistling Paper

You'll need: ■ Looseleaf paper (to begin) ■ Scissors ■ A pencil

Make a whistle out of a piece of paper. How? Get some looseleaf paper and cut a strip about six inches long and two inches wide. Fold it in half (widthwise), and in the middle of the fold poke a pencil all the way through the paper. Fold it in half again, touch the two outside flaps (but don't smash them together), and blow through the folds. Be careful, this can be much louder than you would ever think a piece of paper could get! Try this with different size holes, different types of paper (file folders, tissue paper, index cards), and with different people.

—Jennifer White

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